The use of hydrazones for efficient mannich type coupling with aldehydes and secondary amines

Valérie Atlan, Hugues Bienaymé, Laurent El Kaim* and Adinath Majee

Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75015 Paris, France. E-mail: elkaim@ensta.fr

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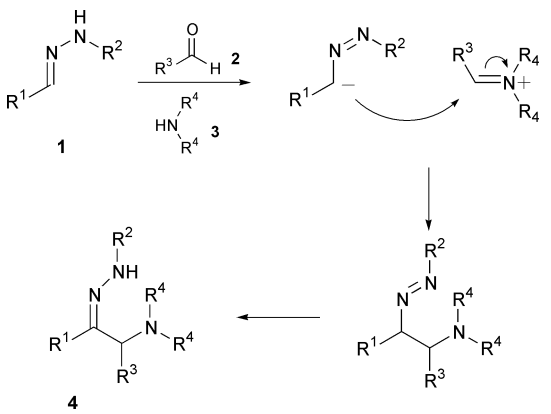
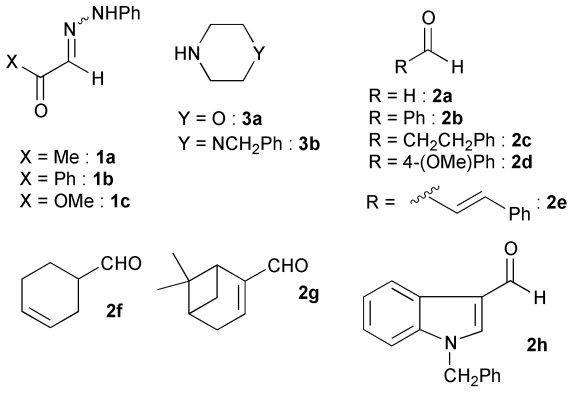
The Mannich reaction of hydrazones originally limited to the coupling of hydrazones with formaldehyde has been extended to a large variety of aldehydes through appropriate selection of experimental conditions; in conjunction with the Japp–Klingmann reaction, this process provides an efficient synthetic tool for the formation of carbon–carbon bonds.

The Mannich reaction is one of the most widely used reactions for the formation of carbon–carbon bonds. In its initial form, it implied the addition of aldehydes to ketones in the presence of amines.[1] The scope of the Mannich reaction was then extended to the addition of different carbon nucleophiles such as nitro compounds.[2] The ease of deprotonation of monosubstituted hydrazones **1** under basic conditions is dependent upon the attached substituents. The resulting salt can be viewed as an aza-substituted carbanion and as such may interact in a Mannich reaction leading to carbon–carbon bond formation (Scheme 1). Indeed in 1957, Keil and Ried[3] reported such behavior but their study revealed only modest synthetic potential as moderate to good yields were only obtained with formaldehyde; furthermore the hydrazones needed an electron withdrawing group (R^1) tethered to the carbonyl function. The potential of this reaction has led us to perform a more extensive study and we were delighted to find that different experimental conditions and the appropriate selection of the amine permit the condensation of hydrazones **1** with many different aldehydes **2** (Table 1, Scheme 1) giving the new aminohydrazones **4** in good yields. Most noteworthy are the good yields obtained with several aliphatic aldehydes possessing α-hydrogens. For the latter, competing aldol type reactions usually preclude their efficient use in Mannich reactions.[4] The first indication of success probably came from the choice of *N*-benzylpiperazine as the amine partner in this reaction. A net increase in yield is observed in going from aliphatic amine to morpholine and finally to *N*-benzylpiperazine. The reaction is best performed in a concentrated toluene solution (2 M) at 80 °C with nearly equimolar amounts of aldehyde (1.1 eq.) and amine (1.1 eq.).

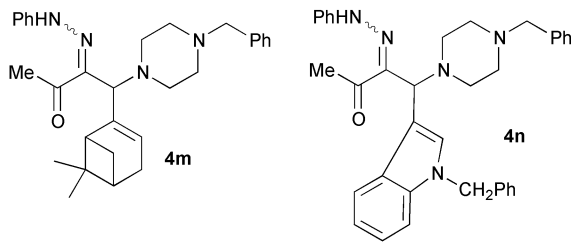
The main drawback of this reaction is, as observed by Reid and Keil,[3] the need for an electron withdrawing group tethered to the hydrazone functionality. This limitation on the starting hydrazones is however deeply counter-balanced by their easy access *via* the Japp–Klingmann reaction between β-ketoacids and diazonium salts (Scheme 2).



Scheme 1



	X	Y	R
4a	Me	O	H
4b	Me	NCH_2Ph	H
4c	Me	O	Ph
4d	Me	NCH_2Ph	Ph
4e	Me	O	$(CH_2)_2Ph$
4f	Me	NCH_2Ph	CH=CHPh
4g	Ph	NCH_2Ph	H
4h	OMe	O	Ph
4i	OMe	O	$(CH_2)_2Ph$
4j	OMe	NCH_2Ph	4-(OMe)Ph



Since the use of *N*-benzylpiperazine leads to good yields of product, a clean way to displace this group becomes crucial for the synthetic potential of this reaction. The chemistry of azoalkenes brings us a possible answer to this problem: treatment of hydrazone **4g** in various alcohols with two equivalents of 1,2-dibromoethane under reflux generates the new ether **5** probably *via* an azoalkene trapping by the alcohol (Scheme 3); hydrazone **4b** behaves similarly. This substitution process needs an alcohol with a rather high boiling point (at

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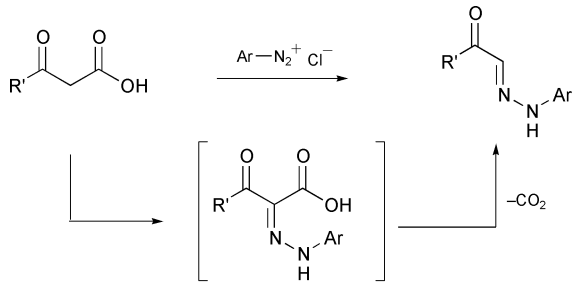
Table 1 Mannich reaction of hydrazones **4**

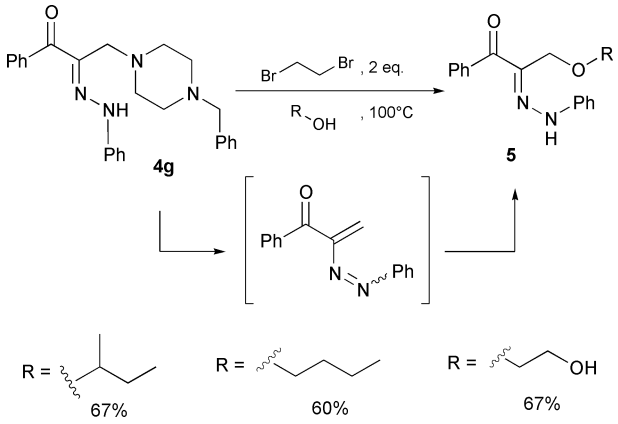
Hydrazone	Aldehyde	Amine	Product[a]	Time	Yield (%)
1a	**2a**	**3a**	**4a**	0.5 h[b]	60
1a	**2a**	**3b**	**4b**	1 h[b]	96
1a	**2b**	**3a**	**4c**	14 h[c]	58
1a	**2b**	**3b**	**4d**	5 h[c]	76
1a	**2c**	**3a**	**4e**	2 h[c]	73
1a	**2e**	**3b**	**4f**	3 h[c]	74
1b	**2a**	**3b**	**4g**	2.5 h[b]	92
1c	**2b**	**3a**	**4h**	6 h[c]	50
1c	**2c**	**3a**	**4i**	6 h[c]	30
1c	**2d**	**3b**	**4j**	8 h[c]	46
1a	**2f**	**3b**	**4k**	3.5 h[c]	79
1b	**2f**	**3b**	**4l**	9 h[c]	65
1a	**2g**	**3b**	**4m**	10 h[c]	35
1a	**2h**	**3b**	**4n**	8 h[d]	72

[a] The NMR spectra (C13, DEPT-135) of all products show that the Mannich condensations have taken place at carbon and not at the nitrogen of the ambident system. [b] Addition of 1.1 eq. aldehyde, 1.1 eq. amine to a 3 M solution of hydrazone in refluxing ethanol. [c] Addition of 1.1 eq. aldehyde, 1.1 eq. amine to a 2 M solution of hydrazone in toluene at 80 °C. [d] Addition of 1.1 eq. aldehyde, 1.1 eq. amine to a 2 M solution of hydrazone in refluxing toluene.



Scheme 2

least 100 °C) as no reaction is observed in MeOH or EtOH. The use of 1,2-dibromoethane seems to be important for elimination of the piperazine unit; MeI reacts cleanly with hydrazone **4b** in ethanol giving a salt that does not react in refluxing EtOH or



Scheme 3

reacts sluggishly in higher boiling alcohols (the regiochemistry of the alkylation step could be invoked to explain these results).

This 1,2-dibromoethane assisted elimination procedure further emphasises the potential of the preceding Mannich reaction as many fruitful applications of transient azoalkenes (cycloadditions to give various heterocycles, Michael additions, *etc*.) have been reported in the literature[5] and could be applied to the Mannich addition products. These features and the selectivity of the 1,2-dibromoethane alkylation are currently being studied in our research group and will be reported soon.

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Notes and references

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